PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Briggs and Tatum

Serial No. 09/210,747

Filed: December 15, 1998

Group Art Unit: 1641

Examiner: V. Portner

Atty. Dkt. No. 295.77957

For: **CONSTRUCTION OF *PASTEURELLA HAEMOLYTICA* VACCINES**

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BRIEF ON APPEAL

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

An original and two copies of this brief are submitted along with the fee of $300.00. Appellants filed the Notice of Appeal on June 7, 2000. We believe no petition for extension of time or fee is necessary to make this brief timely filed. If a fee is required, please charge our Deposit Account No. 19-0733.

REAL PARTIES IN INTEREST

The real parties in interest in this application are the United States of America Department of Agriculture and the Biotechnology Research and Development Corporation, to which this invention is assigned.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF CLAIMS

Claims 1-33, 36, and 37 are canceled. Claims 34, 35, and 38-50 stand rejected. Claims 34, 35, and 38-50 are appealed.

STATUS OF AMENDMENTS

Appellants filed an amendment on April 7, 2000, which was not entered. An Advisory Action mailed June 6, 2000 indicated that the amendment would not be entered upon filing an appeal.

SUMMARY OF THE INVENTION

The invention is a vaccine to induce protective immunity against *Pasteurella haemolytica* infection. The vaccine comprises an isolated *P. haemolytica* bacterium which comprises a mutation in one of the following genes: *aro*A, *Pha*I, leukotoxin C, leukotoxin A, leukotoxin B, leukotoxin D, or neuraminidase. The vaccine may contain an adjuvant and may be formulated for intranasal, intratracheal, intramuscular, subcutaneous, or intravenous administration.

ISSUES

1. **Gentry *et al.* does not anticipate claims 34, 38, 39, and 46-49 because it neither expressly nor inherently discloses a *P. haemolytica* bacterium comprising a mutation in a leukotoxin gene.**

2. **Cruz *et al.* does not anticipate claims 34, 38, 39, and 47 because it neither expressly nor inherently discloses a *P. haemolytica* bacterium comprising a mutation in the leukotoxin A gene.**

3. **Homchampa *et al.* does not render claims 34, 35, 38, 39, and 41-44 obvious because one of ordinary skill in the art would not have been able to use the teachings in Homchampa *et al.* to introduce exogenous DNA into *P. haemolytica* at the time the parent application was filed.**

4. **Because Appellants filed a Terminal Disclaimer to remove the judicial obviousness-type double-patenting rejection of claims 34, 35, and 38-44, the rejection should be withdrawn.**

5. **Because claim 40 is not directed to the same invention as claim 12 of U.S. Patent 5,587,305, the statutory double patenting rejection of claim 40 is improper.**

6. **Because Appellants limited claims 34, 35, and 38-50 to subject matter which the Patent Office acknowledges is enabled, the enablement rejection is improper.**

7. **Claims 38, 39, 43, and 44 are definite.**

GROUPING OF CLAIMS

Claims 34, 35, and 38-50 are grouped as follows:

- claims 34, 38, 39, and 46-49 stand or fall together with respect to the rejection under 35 U.S.C. § 102(b) over Gentry *et al.*;
- claims 34, 38, 39, and 47 stand or fall together with respect to the rejection under 35 U.S.C. § 102(b) over Cruz *et al.*;
- claims 34, 35, 38, 39, and 41-44 stand or fall together with respect to the rejection under 35 U.S.C. § 103(a) over Homchampa *et al.*;
- claims 34, 35, and 38-44 stand or fall together with respect to the rejection for judicial obviousness type double patenting;
- claim 40 stands or falls alone with respect to the rejection under 35 U.S.C. § 101;
- claims 34, 35, and 38-50 stand or fall together with respect to the rejection under 35 U.S.C. § 112, first paragraph; and
- claims 38, 39, 43, and 44 stand or fall together with respect to the rejection under 35 U.S.C. § 112, second paragraph.

ARGUMENT

1. Gentry *et al.* does not anticipate claims 34, 38, 39, and 46-49 because it neither expressly nor inherently discloses a *P. haemolytica* bacterium comprising a mutation in a leukotoxin gene.

Claims 34, 38, 39, and 46-49 stand rejected under 35 U.S.C. § 102(b) as anticipated by Gentry *et al.*, *Veterinary Microbiol. 16*, 351-67 (1988). Gentry *et al.* is cited as disclosing strains of *Pasteurella haemolytica* which produced various degrees of toxicity when administered as a composition to cattle. The Office Action asserts that "[t]he variation evidenced by each of the five [sic, six] strains is indicative of differences in the genetic make up of each of the leukotoxins and therefore represent naturally occurring mutations present in Pasteurella haemolytica strains." Page 5, lines 1-5. The Final Office Action then leaps to the conclusion that Gentry *et al.* anticipates the vaccine of claims 34, 38, 39, and 46-49. There is, however, no basis in Gentry *et al.* or in the law for such a conclusion.

Anticipation under 35 U.S.C. § 102 requires that "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Gentry *et al.* does not meet this standard. Gentry *et al.* does not expressly describe "an isolated *Pasteurella haemolytica* bacterium which comprises a mutation in a gene selected from the group consisting of *aro*A, *Pha*I, leukotoxin C, leukotoxin A, leukotoxin B, leukotoxin D, and neuraminidase," as independent claim 34 requires. Gentry *et al.* describes five different serotypes and one untypable (UT) strain of *P. haemolytica*. See paragraph bridging pages 352 and 353. It provides no description of any mutation in any *aro*A, *Pha*I, leukotoxin, or neuraminidase gene in any of these six strains. Clearly, Gentry *et al.* does not expressly describe a *P. haemolytica* bacterium comprising a mutation in one of the recited genes.

Gentry *et al.* also does not inherently describe the subject matter to which claims 34, 38, 39, and 46-49 are directed. To establish inherency, extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2d 1746, 1759 (Fed. Cir. 1991) (emphasis added). The Final Office Action baldly asserts that "[t]he variation evidenced by each of the five strains is indicative of differences in the genetic make up of each of the leukotoxins and therefore represent naturally occurring mutations present in Pasteurella haemolytica strains." Final Office Action at page 5, lines 1-4.

The conclusion of the Final Office Action is mere speculation. The variation described in Gentry *et al.* quite clearly is not a description of a *P. haemolytica* bacterium comprising a mutation in one of the recited genes which is necessarily present and which would be so recognized by persons of ordinary skill, as required by the standard set forth in *Continental Can Co. v. Monsanto.* Contrary to the Final Office Action's speculation, Gentry *et al.* does not attribute observed differences in *in vivo* toxicity of the disclosed strains to a difference in the "genetic make up" of their leukotoxin molecules. In fact, Gentry *et al.* teaches exactly the opposite.

First, Gentry *et al.* teaches that a leukotoxin mutation is not the probable cause of lowered toxicity. The *P. haemolytica* strains disclosed in Gentry *et al.* were not variably toxic under all circumstances. Gentry *et al.* teaches that "[n]one of the strains was found to be significantly more or less toxic *in vitro* than the others at a majority of the dilutions tested (P>0.05)." Gentry *et al.* at page 362. Despite its toxicity *in vitro*, the UT strain was less pathogenic *in vivo* than the other strains tested. Gentry *et al.* points to factors other than leukotoxin production as being responsible for this difference: "That the UT strain was as toxic in the in vitro assay as the remainder of the organisms indicates that its inability to produce lesions in vivo may have been due to a deficiency

in some pathogenic parameter other than leukotoxin production." *Id.* This clear teaching in Gentry *et al.* precludes an interpretation of the UT strains' lower *in vivo* toxicity as necessarily, or even likely, due to alterations in leukotoxin molecules, as asserted in the Final Office Action.

Second, Gentry *et al.* teaches that its results support a recent study which concluded "that differences in the frequency of isolation of [four of the] serotypes was not due to differences in virulence of the organisms." Rather, "subtle differences in growth rates or ability to maintain stationary phase in vitro as shown in the present study, may indicate selective disadvantage for certain strains of *P. haemolytica* for disease production." Gentry *et al.*, paragraph bridging pages 364-65. Again, Gentry *et al.* teaches that it is not even likely that genetic differences in leukotoxin molecules are involved in the observed differences in toxicity. Gentry *et al.* states that differences in "some other pathogenic parameter" or differences in growth rates or ability to maintain stationary phase *in vitro* may be responsible for these differences. This teaching is in direct contradiction to the Final Office Action's unfounded assumption that Gentry discloses *P. haemolytica* with "differences in the genetic make up of each of the leukotoxins."

Third, Gentry *et al.* carried out cross-neutralization studies of leukotoxin-neutralizing antibodies produced in cattle in a vaccination trial. "It was determined that there was no strain specificity shown with regard to type of leukotoxin neutralized." Gentry *et al.* at page 363. A lack of strain specificity regarding leukotoxin neutralization is evidence that the leukotoxins of the strains tested are similar, rather than "genetically different," as asserted in the Final Office Action. Again, Gentry *et al.*'s results do not support the Final Office Action's speculation.

The Final Office Action's "genetic make-up" theory is, at best, only a possible explanation for the differences in toxicity exhibited by the disclosed *P. haemolytica* strains. It is well established, however, that inherency "may not be established by probabilities or possibilities. The

mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981).

In asserting that Gentry *et al.* anticipates claims 34, 38, 39, and 46-49, the Patent Office has ignored the well established case law that a reference under 35 U.S.C. § 102 must explicitly or inherently disclose each element of the claims. Gentry *et al.* does not meet these requirements and therefore does not anticipate claims 34, 38, 39, and 46-49. The rejection should be withdrawn.

2. Cruz *et al.* does not anticipate claims 34, 38, 39, and 47 because it neither expressly nor inherently discloses a *P. haemolytica* bacterium comprising a mutation in the leukotoxin A gene.

Claims 34, 38, 39, and 47 stand rejected under 35 U.S.C. § 102(b) as anticipated by Cruz *et al.*, *Mol. Microbiol. 4*, 1933-39 (1990). Cruz *et al.* is cited as disclosing strains of *Pasteurella haemolytica* comprising internal deletions in the leukotoxin A gene. The Patent Office takes the position that such strains inherently have the characteristics of the claimed vaccines and therefore anticipate claims 34, 38, 39, and 47.

As discussed above, an anticipatory reference must disclose, either explicitly or inherently, each element of the invention. *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 771, 218 U.S.P.Q. 781, 789 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). Cruz *et al.* does not even remotely satisfy this requirement.

Cruz *et al.* discloses plasmids derived from plasmid pYFC19 which contain a *P. haemolytica lktA* gene comprising an internal deletion. Cruz *et al.* at page 1938, column 1, first full paragraph. Cruz *et al.* expressed the leukotoxin protein from the modified plasmid in an *E. coli* host (TB1). Paragraph spanning pages 1937 and 1938 and page 1938, column 2, paragraph 1.

Cruz *et al.* also discloses *P. haemolytica* biotype A, serotype 1 and expression of native

leukotoxin from this bacterium. Cruz *et al.* at page 1937, column 2, last paragraph, and page 1938, column 1, last paragraph. Native leukotoxin is by definition wild-type, *i.e.*, it does not comprise a mutation as required in claims 34, 38, 39, and 47.

Contrary to the assertion of the rejection, Cruz *et al.* does not disclose a single strain of *P. haemolytica* which contains the *lktA* gene with the internal deletion. As stated above, to qualify as an inherent disclosure, it must be "clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d at 1268, 20 U.S.P.Q.2d at 1759, emphasis added. Cruz *et al.*'s disclosure of an *E. coli* cell comprising an *lktA* gene with an internal deletion is simply not a disclosure of a *P. haemolytica* bacterium comprising a mutation in a leukotoxin A gene, as recited in claims 34, 38, 39, and 47. Cruz *et al.*'s disclosure of a *P. haemolytica* bacterium expressing native leukotoxin also is not a disclosure of a *P. haemolytica* bacterium comprising a mutation in a leukotoxin A gene, as recited in claims 34, 38, 39, and 47. An *E. coli* bacterium comprising the plasmid with *lktA* deletion and a *P. haemolytica* bacterium expressing native leukotoxin are two separate and distinct entities. The Final Office Action improperly combines these separate and distinct teachings to "make" the vaccines recited in claims 34, 38, 39, and 47. But Cruz *et al.* does not actually teach the subject matter of claims 34, 38, 39, and 47.

In asserting that Cruz *et al.* anticipates claims 34, 38, 39, and 47, the Patent Office has ignored the well established case law that a reference under 35 U.S.C. § 102 must explicitly or inherently disclose each element of the claims. Cruz *et al.* does not meet these requirements and therefore does not anticipate claims 3 34, 38, 39, and 47. The rejection should be withdrawn.

3. **Homchampa *et al.* does not render claims 34, 35, 38, 39, and 41-44 obvious because one of ordinary skill in the art would not have been able to use the teachings in Homchampa *et al.* to introduce exogenous DNA into *P. haemolytica* at the time the parent application was filed.**

Claims 34, 35, 38, 39, and 41-44 stand rejected under 35 U.S.C. § 103(a) as obvious over the teachings of Homchampa *et al.*, *Mol. Microbiol. 6*, 3585-93 (1992). Obviousness is a question of law based on findings of fact. *Graham v. John Deere Company*, 383 U.S. 1, 17-18, 148 U.S.P.Q. 459, 467 (S. Ct. 1966). An obviousness analysis requires determination of certain facts:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved.

Id. When Appellants' claims are compared with the scope and content of Homchampa *et al.*, it is clear that claims 34, 35, 38, 39, and 41-44 are not obvious.

Homchampa *et al.* is cited as teaching an attenuated *aro*A mutant of *Pasteurella multocida* which was produced by insertion of a kanamycin-resistance gene into the *aro*A gene. Office Action mailed February 19,1999, paragraph bridging pages 9 and 10. Homchampa *et al.* also is cited as disclosing a vaccine composition which provided mice with complete protection against a lethal dose of *Pasteurella multocida*. *Id.* In contrast, claims 34, 35, 38, 39, and 41-44 are directed to vaccines comprising an isolated *Pasteurella haemolytica* bacterium which contains a mutation in one of a recited group of genes. As the Office Action acknowledges, *Pasteurella haemolytica* and *Pasteurella multocida* are different bacteria.

Nonetheless, the Office Action asserts that it would have been obvious to have used the techniques, methods, and genes taught by Homchampa *et al.* to make an attenuated live mutant of *Pasteurella haemolytica* to obtain a vaccine composition. To make a *prima facie* case that claims

34, 35, 38, 39, and 41-44 are obvious over Homchampa *et al.*, however, the Patent Office must show that the prior art contains a suggestion or motivation to modify its teachings to make Appellants' claimed vaccines. (*See* § 2143 of the Manual of Patent Examining Procedure, 7th ed., Rev. 1, February 2000).

The Office Action implies that the motivation to make a *Pasteurella haemolytica* vaccine is based on the high degree of homology of the *P. multocida aro*A gene and *aro*A genes from other bacteria. Homchampa *et al.* provides an alignment of the deduced amino acid sequences encoded by four *aro*A genes (from *E. coli*, *Salmonella typhimurium*, *Y. enterocolitica;* and *B. pertussis*) with the amino acid sequence of aroA from *P. multocida*. See Fig. 4 at page 3589. Homchampa *et al.* also mentions the "high degree of amino acid sequence conservation" among several bacterial and eukaryotic *aro*A proteins. In spite of this acknowledgment of sequence similarity, however, Homchampa *et al.* does not teach or suggest that its teachings could be extended beyond construction of *P. multocida* vaccines. Homchampa *et al.* teaches only that "[t]he data presented here support the use of rational attenuation as a means of constructing non-reverting, live vaccine strains of *P. multocida*." See page 3591, column 1, first full paragraph. There is no suggestion in Homchampa *et al.* that the homologies shown in Fig. 4 would have motivated one of ordinary skill in the art to have constructed a *Pasteurella haemolytica* comprising a mutation in the *aro*A gene, as recited in claims 34, 35, 38, 39, and 41-44. *Pasteurella haemolytica* is not even mentioned in Homchampa *et al.* There also is no suggestion in Homchampa *et al.* that if such a bacterium were constructed it would be useful "to induce protective immunity against *Pasteurella haemolytica* infection," as recited in claims 34, 35, 38, 39, and 41-44.

Moreover, based on the state of the art at the priority date of the present application,[1] the ordinary artisan would not have been motivated to modify the teachings of Homchampa *et al.* as postulated in the Office Action because the ordinary artisan would have had no reasonable expectation of success. Prior to the discovery of the present inventors of the restriction-modification system called *PhaI*, those of ordinary skill in the art were not able to introduce exogenous DNA into *Pasteurella haemolytica*. Workers in the *Pasteurella haemolytica* field had tried to transform the organism with foreign DNA unsuccessfully. The failure was noted in the literature for over a decade prior to the present invention. As stated by Azad *et al.*, *Journal of General Microbiology,* 138, 1185-96 (1992), "Previous investigators have reported that the recovery of *P. haemolytica* Ap^R plasmids from *E. coli* transformants was either poor (Livrelli *et al.,* 1988; Craig *et al.,* 1989) or non-existent (Zimmerman & Hirsh, 1980). Similar results were obtained in this study . . . ." Azad at page 1195.

Craig *et al.*, *Journal of General Microbiology* 135, 2885-90 (1989), suggested that the reason for failure to introduce DNA from a variety of conjugative, suicide shuttle vectors able to replicate in *E. coli* may be due to the capsular layer of *P. haemolytica*. Craig stated:

> *P. haemolytica* T179 (serotype A1) and *P. haemolytica* Y216 (serotype A2) are encapsulated organisms (Gilmour *et al.*, 1985), and the capsule may have interfered with the entry of DNA by freeze-thaw or heat-shock transformation. Attempts to generate unencapsulated strains of *P. haemolytica* by chemical (*N*-methyl-*N*'-nitro-*N*-nitrosoguanidine) mutagenesis were unsuccessful but a spontaneously occurring strain (*P. haemolytica* Y216/NS1) with a reduced amount of capsule was isolated. This capsular-deficient strain, however, was still resistant to transformation by $CaCl_2$-mediated techniques.

Craig at page 2889. Thus, workers in the art came up against the barrier to transformation of *P. haemolytica* and for years were unable to solve it. The inventors' solution of finding a restriction-

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[1] The present application is a continuation of Serial No. 08/643,299 filed May 8, 1996 (now issued as U.S. Patent 5,849,305), which is a division of Serial No. 08/162,392 filed December 6, 1993 (now issued as U.S. Patent 5,587,305).

modification system was not at all obvious to those of skill in the art. As shown above, Craig postulated a totally different reason for the inability to transform *P. haemolytica*.

Before the parent application to the present application was filed, there was a great need in the art for means of manipulating *P. haemolytica,* and there was a recognized difficulty in doing so. Nonetheless, the workers in the field were not clear as to what the solution to the problem would be. Thus, application of the methods of Homchampa directly to *Pasteurella haemolytica* would have been to no avail. Appellants pursued a solution to this problem and were successful in overcoming the barrier to transformation in this organism. Without the methods and reagents taught in the present invention, one of ordinary skill in the art could not have achieved the vaccine compositions of claims 34, 35, 38, 39, and 41-44.

The non-obviousness of the method used to achieve transformation of *P. haemolytica* is affirmed by prior decisions of the U.S. Patent and Trademark Office in related applications:

- U.S. Patent 5,587,305 claims the method of making mutants of *Pasteurella haemolytica* which employs using *Pha*I methyltransferase, a methylating enzyme which recognizes the *PhaI* restriction site, *Pasteurella haemolytica* transformants made by that method, and the strain NADC-D60aroA$^-$.
- U.S. Patent 5,849,305 claims a vaccine for subcutaneous administration comprising an attenuated, live mutant of *P. haemolytica* comprising an *aro*A mutation introduced using *Pha*I.

The obstacle of transforming *Pasteurella haemolytica* was truly formidable. The Patent Office acknowledged the patentability of Appellants' method of overcoming this obstacle by issuing the patents cited above. In fact, the Examiner's Reasons for Allowance of Serial No. 08/643,299 (issued as U.S. Patent 5,489,305) states, "The prior art does not teach or reasonably suggest the use

of a PhaI restriction site in Pasteurella haemolytica for the formulation of an AroA mutant strain which is effective in the treatment of cattle." One of ordinary skill in the art at the time Appellants made this invention clearly would not have expected that the techniques taught by Homchampa *et al.* for use in *P. multocida* could have been used to make the vaccines of claims 34, 35, 38, 39, and 41-44.

It is well known that the suggestion to modify a reference teaching "must be founded in the prior art, not in applicant's disclosure." *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). It is Appellants' disclosure, however, which teaches how to introduce exogenous DNA into *P. haemolytica*. It is also Appellants' disclosure which teaches that a *Pasteurella haemolytica* bacterium comprising an *aro*A mutation is useful to induce protective immunity against *Pasteurella haemolytica* infection. Reading this teaching into the prior art is pure hindsight reconstruction, and the Federal Circuit has firmly rejected this practice. *See, e.g., In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1599-1600 (Fed. Cir. 1988).

The Patent Office has failed to carry its burden of establishing that claims 34, 35, 38, 39, and 41-44 are *prima facie* obvious over the teachings of Homchampa *et al.* The rejection should be reversed.

4. Because Appellants filed a Terminal Disclaimer to remove the judicial obviousness-type double-patenting rejection of claims 34, 35, and 38-44, the rejection should be withdrawn.

The Final Office Action maintained a judicial obviousness-type double patenting rejection of claims 34, 35, and 38-44 over claims 1-4 of U.S. Patent 5,849,305 and claim 5 of U.S. Patent 5,824,525. On April 7, 2000, Appellants filed a Terminal Disclaimer. The Advisory Action mailed June 6, 2000, however, did not indicate that the judicial obviousness-type double patenting rejection

had been withdrawn.

The filing of the Terminal Disclaimer overcomes a judicial obviousness-type double patenting rejection. *In re Vogel and Vogel*, 422 F.2d 438, 442, 164 U.S.P.Q. 619, 622 (C.C.P.A. 1970). The Board should therefore direct the Examiner to remove the rejection.

5. Because claim 40 is not directed to the same invention as claim 12 of U.S. Patent 5,587,305, the statutory double patenting rejection of claim 40 is improper.

Claim 40 stands rejected under 35 U.S.C. § 101 as claiming the same invention as claim 12 of U.S. Patent 5,587,305. For double patenting purposes, "the same invention" means "identical subject matter." *In re Vogel and Vogel*, 422 F.2d 438, 441, 164 U.S.P.Q. 619, 621 (C.C.P.A. 1970). The test for whether two claims are directed to the same invention is stated in *In re Vogel*:

> A good test, and probably the only objective test, for "same invention," is whether one of the claims could be literally infringed without literally infringing the other. If it could be, the claims do not define identically the same invention.

Id., 164 U.S.P.Q. at 622. Application of this test clearly reveals that claim 12 of U.S. Patent 5,587,305 and claim 40 of the appealed application do not define the same invention.

Rejected claim 40 and issued claim 12 are compared in the table below.

pending claims 34 and 40	issued claim 12
34. A vaccine to induce protective immunity against *Pasteurella haemolytica* infection, comprising: an isolated *Pasteurella haemolytica* bacterium which comprises a mutation in a gene selected from the group consisting of *aro*A, *Pha*I, leukotoxin C, leukotoxin A, leukotoxin B, leukotoxin D, and neuraminidase. 40. The vaccine of claim 34 comprising *P. haemolytica* ATCC 55518.	12. *P. haemolytica* strain NADC-D60aroA$^-$, deposited at the ATCC as Accession No. ATCC 55518.

Rejected claim 40 is dependent on claim 34 and therefore is directed to a vaccine to induce protective immunity against *Pasteurella haemolytica* infection, comprising *P. haemolytica* ATCC 55518. Claim 12 of U.S. Patent 5,587,305 is directed simply to "*P. haemolytica* strain NADC-D60aroA$^-$, deposited at the ATCC as Accession No. ATCC 55518."

Issued claim 12 can be literally infringed without infringing rejected claim 40. For example, a histological preparation of ATCC 55518, affixed to a glass microscope slide and stained so that one could visualize the bacteria under the microscope, would literally infringe claim 12 because the histological preparation contains the bacterium ATCC 55518. The same histological preparation of ATCC 55518, however, would not literally infringe claim 40, because such a preparation is not "a vaccine to induce protective immunity against *Pasteurella haemolytica* infection." For example, the specification contains the following teaching about the claimed vaccine:

> Vaccines are typically formulated using a sterile buffered salt solution. Sucrose and/or gelatin may be used as stabilizers, as is known in the art. It is desirable that the *P. haemolytica* vaccines of the invention be administered by the intranasal or intratracheal route, but subcutaneous, intramuscular, intravenous injections also may be

used.

Pate 9, lines 17-21. The histological preparation of ATCC 55518, affixed to a glass microscope slide and stained, could not be administered by any of the means taught in the specification to induce protective immunity against *P. haemolytica* infection. The histological preparation is not sterile, nor could it comprise stabilizers or adjuvants.

Under the test set forth in *In re Vogel* (whether one claim could be literally infringed without literally infringing the other), rejected claim 40 clearly does not claim "the same invention" as claim 12 of U.S. Patent 5,587,305. The statutory double patenting rejection of claim 40, therefore, is improper and should be withdrawn.

6. Because Appellants limited claims 34, 35, and 38-50 to subject matter which the Patent Office acknowledges is enabled, the enablement rejection is improper.

The Office Action mailed February 19, 1999 rejected claims 34-37, stating:

> [T]he disclosure is enabling only for claims limited to site directed mutations of *Pasteurella haemolytica* using aroA, PhaI, leukotoxin operon (C, A, B, D), and neuraminidase genes, and specific compositions for the treatment of cattle and sheep.

Page 4, third paragraph. The Office Action asserted that "the claims recite the use of any region of the genome from *Pasteurella haemolytica*" but that "the specification is silent on how to use **any** region of the genome for producing a mutation to yield the desired result." Page 4, fourth paragraph (emphasis in original).

To advance prosecution, Appellants limited claim 34 to vaccines comprising an isolated *Pasteurella haemolytica* bacterium which "comprises a mutation in a gene selected from the group consisting of *aro*A, *Pha*I, leukotoxin C, leukotoxin A, leukotoxin B, leukotoxin D, and neuraminidase." The genes recited in this Markush group are those in which the Office Action stated

that mutations were enabled.

Despite this amendment, the Final Office Action maintained the enablement rejection of claims 34 and 35 and applied it as well to newly added claims 38-50.[2] The Final Office Action did not acknowledge that Appellants limited claim 34 to the enabled Markush group, stating that "The claims are NOT limited to the introduction of DNA into the genes which encode the recited proteins but any type of mutation is recited."[3]

Recitation of the Markush group should have been sufficient to remove the rejection under 35 U.S.C. § 112, first paragraph, with respect to enablement across the full scope of the claims. Section 112, first paragraph, of 35 U.S.C. requires that the specification teach "any person skilled in the art to which [the invention] pertains, or with which it is most nearly connected, to make and use the same . . . ." The present specification meets this standard with respect to claims 34, 35, and 38-50.

Claim 34, as amended July 19, 1999, recites "A vaccine to induce protective immunity against *Pasteurella haemolytica* infection, comprising: an isolated *Pasteurella haemolytica* bacterium which comprises a mutation in a gene selected from the group consisting of *aro*A, *Pha*I, leukotoxin C, leukotoxin A, leukotoxin B, leukotoxin D, and neuraminidase." The specification teaches that mutations in these particular genes are desirable at page 7, lines 4-12:

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[2] Appellants canceled claims 36 and 37.

[3] Appellants believe the Final Office Action may have focused on remarks which inadvertently conflicted with another amendment to claim 34 made in the amendment filed July 19. That amendment deleted a recitation originally present in claim 34, which specified that the recited mutation is "introduced into *P. haemolytica* using methylated DNA." Appellants' remarks, without deceptive intent, erroneously referred to the recitation as if it were still present in the claim. See page 5, paragraph 3. Possibly the Final Office Action focused on the resulting discrepancy between Appellants' remarks and the amendment to claim 34 and did not notice the recitation of the enabled Markush group.

> Site-directed mutagenesis of *P. haemolytica* can be accomplished according to the present invention by first isolating a wild-type DNA region from *P. haemolytica*. As described below in the examples, an *aro*A gene can be isolated using *aro*A DNA from other bacteria as hybridization probes. The sequence of the *P. haemolytica aro*A gene is shown in SEQ ID NO. 1. Similarly other genes can be isolated from *P. haemolytica*. Another desirable gene for mutations is the *Pha*I endonuclease gene, which is provided in *Pha*IMtase (ATCC Accession No. ATCC 69500). Other genes in which mutations may be desirable are genes in the leukotoxin operon (C, A, B, D) and neuraminidase.

The specification also teaches how to introduce exogenous DNA, including mutated DNA, into *P. haemolytica:* "a barrier to transformation of *P. haemolytica* can be overcome by treating DNA with a methylating enzyme, such as the *Pha*I methyltransferase." Specification at page 6, lines 15-17. Methylation of DNA substrates for transformation is taught at page 6, line 25, to page 7, line 3. The specification also teaches that the particular method of introducing mutations into DNA to be inserted into *P. haemolytica* is not critical:

> A mutation is created in the isolated, wild-type DNA region according to any method known in the art. For example, the isolated DNA can be chemically mutagenized, either in a bacterium or *in vitro*. Alternatively, restriction endonucleases can be used to create precise deletions or insertions *in vitro*. Other methods as are known in the art can be used as is desirable for a particular application.

Page 7, lines 12-17. Creating mutations in the recited genes was well within the skill of the art at the priority date of the present application. The specification is not required to teach the art what is well known. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986).

The specification teaches how to introduce the mutated, methylated DNA into *P. haemolytica* bacteria at page 7, line 19, to page 8, line 23. Working examples 1-6 provide detailed instructions which one of skill in the art of bacterial genetic engineering can easily follow to make the claimed

vaccines. Provided with the teachings of the specification, together with the general knowledge in the art of bacterial genetic engineering, one of skill in the art could easily practice the invention of claims 34, 35, and 38-50.

Moreover, the Patent Office acknowledged twice during this prosecution that the specification enables vaccines comprising a *P. haemolytica* bacterium comprising a mutation in a gene of the recited Markush group. See the passage from the Office Action mailed February 19, 1999, quoted above, as well as page 6, first paragraph, of the Final Office Action:

> [t]he instant specification only provides original descriptive support for compositions which comprise PhaI and AroA mutations which in turn may be in association with other genetic mutations in the leukotoxin C, leukotoxin A, leukotoxin B, leukotoxin D, and neuraminidase genes.

In view of the amendment of claims 34, 35, and 38-50 to recite mutations in genes which the Patent Office acknowledges are enabled, maintenance of the rejection of these claims under 35 U.S.C. § 112, first paragraph, is improper. The rejection should be withdrawn.

7. Claims 38, 39, 43, and 44 are definite.

Dependent claims 38, 39, 43, and 44 stand rejected as indefinite under 35 U.S.C. § 112, second paragraph. These claims recite particular modes of administration: intranasal, intratracheal, intramuscular, subcutaneous, or intravenous routes (claims 38 and 43) or subcutaneous injection (claims 39 and 44). The Final Office Action asserts that these recitations do not further limit the subject matter of the claims on which claims 38, 39, 43, and 44 depend: "a mode of administration does not further define the components present in the composition being claimed and the recitation of an intended use does not define a vaccine component." Final Office Action at page 4.

Under the second paragraph of 35 U.S.C. § 112, the relevant inquiry

> . . . is merely to determine whether the claims do, in fact, set out and circumscribe a particular area with a reasonable degree of precision and particularity. It is here where the definiteness of the language employed must be analyzed -- not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art.[2]
>
> [2] It is important here to understand that under this analysis claims which on first reading -- in a vacuum, if you will -- appear indefinite may upon a reading of the specification disclosure or prior art teachings become quite definite. It may be less obvious that this rule also applies in the reverse, making an otherwise definite claim take on an unreasonable degree of uncertainty. See *In re Cohn*, 438 F.2d 989, 58 CCPA 996 (1971), *In re Hammack*, 427 F.2d 1378, 57 CCPA 1225 (1970).

In re Moore, 439 F.2d 1232, 1235, 58 C.C.P.A. 1042, 1046-47 (1971). The importance of the specification in determining whether the claims are definite also was emphasized in *In re Cohn*, 438 F.2d 989, 993, 58 C.C.P.A. 996, 1001 (C.C.P.A. 1971): "No claim may be read apart from and independent of the supporting disclosure on which it is based."

Applying this standard, claims 38, 39, 43, and 44 are definite. One of skill in the art of vaccine administration would readily understand that vaccines administered by particular routes must be formulated for administration by those routes. The specification teaches that

> [i]t is desirable that the *P. haemolytica* vaccines of the invention be administered by the intranasal or intratracheal route, but subcutaneous, intramuscular, intravenous injection also may be used. Suitable formulations and techniques are taught by Kucera U.S. 4,335,106, Gilmour U.S. 4,346,074, and Berget U.S. 4,957,739.

Page 9, lines 18-22. Thus, the specification points to specific teachings in the art which refer to "suitable formulations" of vaccines for the recited routes of administration. Kucera, U.S. Patent 4,335,106, teaches vaccines that protect bovine, porcine, and ovine species against Pasteurella infections; the vaccines can be administered subcutaneously, intranasally, or intramuscularly.

Column 2, lines 56-64. Kucera teaches that "the vaccines of this invention are prepared by standard, known to the art methods, for example by combining the bacteria with a suitable carrier and/or a stabilizer." Column 4, lines 1-4. Kucera teaches formulation of a suitable stabilizer in column 6, lines 13-36.

Gilmour, U.S. Patent 4,346,074, also teaches a formulation of a Pasteurella vaccine suitable for subcutaneous injection at column 5, lines 1-56. Specifically, heat-killed bacteria are adsorbed onto an aluminum hydroxide gel, and this suspension is emulsified in an equal volume of Bayol F containing 10% Aracel A. See column 5, lines 15-20.

Berget, U.S. Patent 4,957,739, teaches aqueous solutions which are "particularly well suited for intramuscular and subcutaneous injection" at column 9, lines 10-20. Berget also teaches preparations suitable for subcutaneous injection at column 13, line 60, to column 14, line 2, and column 16, lines 6 to 12. Preparation of vaccine compositions also is taught in column 32, line 28 to column 35, line 30. Berget particularly teaches that

> Typically, such vaccines are prepared as injectables. Either as liquid solutions or suspensions solid forms suitable for solution in, or suspension in, liquid prior to injection may also be prepared. The preparation may also be emulsified. The active immunogenic ingredient is often mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol, or the like and combinations thereof. In addition, if desired, the vaccine may contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, or adjuvants which enhance the effectiveness of the vaccine.

Column 33, lines 52-64.

"The question under § 112, second paragraph, is whether the claim language, when read by a person of ordinary skill in the art in light of the specification, describes the subject matter with sufficient precision that the bounds of the claimed subject matter are distinct." *Application of Merat*,

519 F.2d 1390, 1396, 186 U.S.P.Q. 471, 476 (C.C.P.A. 1975). The teachings discussed above were known in the art when the present specification was filed and are specifically pointed to in the specification. One of skill in the art would readily have understood the particularities of the formulations required for each of the routes of administration recited in claims 38, 39, 43, and 44. Claims 38, 39, 43, and 44 therefore are definite.[4] The Board should direct the Examiner to withdraw the rejection of these claims under 35 U.S.C. § 112, second paragraph.

CONCLUSION

For the reasons given above, the rejections of claims 34, 35, and 38-50 under 35 U.S.C. §§ 101, 102, 103, and 112 and the rejection of claims 34, 35, and 38-50 for judicial obviousness-type double patenting are improper. The Board of Patent Appeals and Interferences should reverse the rejections.

Respectfully submitted,

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[4] In fact, Appellants tried to amend claims 38, 39, 43, and 44 to specify explicitly that the vaccines to which these claims are directed are "formulated for" the particular routes of administration recited. The Advisory Action refused entry of these amendments.

APPENDIX I

CLAIMS

34. A vaccine to induce protective immunity against *Pasteurella haemolytica* infection, comprising: an isolated *Pasteurella haemolytica* bacterium which comprises a mutation in a gene selected from the group consisting of *aro*A, *Pha*I, leukotoxin C, leukotoxin A, leukotoxin B, leukotoxin D, and neuraminidase.

35. The vaccine of claim 34 containing an adjuvant.

38. The vaccine of claim 34 which is administered by intranasal, intratracheal, intramuscular, subcutaneous, or intravenous routes.

39. The vaccine of claim 34 which is administered by subcutaneous injection.

40. The vaccine of claim 34 comprising *P. haemolytica* ATCC 55518.

41. A vaccine for inducing protective immunity against *Pasteurella haemolytica* infection, comprising: an isolated *Pasteurella haemolytica* bacterium which comprises an *aro*A mutation.

42. The vaccine of claim 41 containing an adjuvant.

43. The vaccine of claim 41 which is administered by intranasal, intratracheal, intramuscular, subcutaneous, or intravenous routes.

44. The vaccine of claim 41 which is administered by subcutaneous injection.

45. The vaccine of claim 34 wherein the gene is *Pha*I.

46. The vaccine of claim 34 wherein the gene is leukotoxin C.

47. The vaccine of claim 34 wherein the gene is leukotoxin A.

48. The vaccine of claim 34 wherein the gene is leukotoxin B.

49. The vaccine of claim 34 wherein the gene is leukotoxin D.

50. The vaccine of claim 34 wherein the gene is neuraminidase.